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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/751,702	01/05/2004	Elaine I. Tuomanen	044158/273011	2930

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EXAMINER	
MINNIFIELD, NITA M	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
01/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/751,702	TUOMANEN ET AL.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-7 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-7 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicants' amendment filed October 12, 2007 is acknowledged and has been entered. Claims 1-4, 8-14 and 16-67 has been canceled. Claims 5, 7 and 15 have been amended. Claims 5-7 and 15 are now pending in the present application. All rejections have been withdrawn in view of Applicants' amendment to the claims and/or comments, with the exception of those discussed below.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 5-7 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for vaccine composition, for active protection against Streptococcus pneumoniae Serotype 6B, comprising a CbpA truncate protein R1 (SEQ ID NO: 3) or a vaccine composition, for passive protection, comprising anti-R2 antiserum (R2 is a CbpA truncate and is SEQ ID NO: 1), does not reasonably provide enablement for a vaccine for treating or protecting against any and all pneumococcal infections comprising a polypeptide in a pharmaceutically acceptable carrier wherein said polypeptide comprises a variant of SEQ ID NO:4, said variant comprises at least one to15 amino acid substitutions and comprises amino acids 331 to 339, 355 to 365, 367 to 374, 379 to 389 and 409 to 427 of SEQ ID NO: 40, said polypeptide does not bind to choline,

said polypeptide exhibits a tertiary structure as found in a native, full-length CbpA polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

It is noted that the pending claims encompass a myriad of possible variants of SEQ ID NO: 4 also having the specific amino acid sequences of SEQ ID NO: 40 as set forth in claim 1. A review of the specification indicates only one vaccine that treats or protects against pneumococcal infection in a subject. This vaccine composition comprises R1, a truncated N-terminal fragment of CbpA (serotype 4). The specification indicates that amino acid sequence of R1 is set forth in SEQ ID NO: 3. The specification discloses that 80% of the "...mice immunized with CbpA truncate protein R1 survived challenge. All sham immunized mice were dead by day 8 (Figure 7). This data demonstrates that immunization with a recombinant fragment of CbpA elicits production of specific antibodies capable of protecting against systemic pneumococcal infection and death." (see p. 69, l. 12-16) There does not appear to be a vaccine composition comprising the claimed polypeptide, which comprise SEQ ID NO: 4, variants of SEQ ID NO: 4, both having the specific amino acid sequences of SEQ ID NO: 40 as set forth in claim 1. It is not clear if the claimed polypeptide is disclosed in the pending specification, save the description on p. 12 of the specification, which states that polypeptide C/R2 comprising a repeat region C within R2, wherein the repeat region C has the amino acid sequences from position 327 to position 433 of the N-terminal choline binding protein A (CbpA) serotype type 4 (SEQ ID NO: 4). There are no experimental examples that teach that polypeptide C/R2, in a vaccine composition, actively protects against any and all pneumococcal infections in a subject, which pneumococcal infections encompasses pneumonia, meningitis, otitis media, sinusitis, bronchitis, empyema, sepsis, septicaemia, peritonitis and arthritis/osetomyelitis (see Bogaert et al Lancet Infect. Dis., 2004, 4:144-154).

The state of the art with regard to pneumococcal infection and vaccines is unpredictable. Bogaert et al (Vaccine, 2004, 22:2209-2220) teaches that although many proteins, including pneumolysin, PspA, PsaA, CbpA, neuraminidase, pneumococcal surface adhesion A and autolysin have been *suggested as potential candidates*, the proteins PspA, PsaA and pneumolysin are currently the leading vaccine *candidates* (p. 2213). "Other pneumococcal proteins that have shown *potential* as vaccine *candidates* are PspC (CbpA), the Pht family, putative proteinase maturation protein A (PpmA), autolysin and neuraminidase. PspC either contains a choline-binding domain like PspA and pneumolysin or a LPXTG

motif like other gram-positive bacteria (citation omitted). This protein is supposed to bind secretory IgA and to interact with human epithelial and endothelial cells (citations omitted). Vaccination with PspC has shown to be protective against sepsis in mice. Moreover, antibodies directed against this protein have shown cross-reactivity against PspA (citation omitted). It is not yet clear though whether vaccination with PspC elicits protection against heterologous PspC type strains. The Pht family is one of cell surface-exposed homologous proteins representing histidine triad motifs of which several members have shown to elicit protection against different pneumococcal serotypes in a mouse sepsis model (citation omitted)." (Bogaert et al 2004, p. 2215) Protection against sepsis is not an indication that this polypeptide will protect against all pneumococcal infections nor is it to be considered to elicit species-wide pneumococcal infection protection.

It is noted that the claims recite a "variant comprises *at least* one to 15 amino acid substitutions" (see claim 1). It is also noted that the specification teaches that variant encompasses deletions containing less than all of the residues specified for the protein, substitutions wherein one or more residues specified are replaced by other residues and additions wherein one or more amino acid residues are added to a terminal or medial portion of the polypeptide (p. 13). The specification has not taught how to make and use any and all variants of the polypeptide as presently claimed and the polypeptide variants function as a vaccine to protect/treat pneumococcal infection.

Further, the state of the art with regard to variants, analogs and derivatives of polypeptides is unpredictable. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, JCB, 1990, 111:2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduce the biological activity of the mitogen (see Lazar et al, Molecular and Cellular Biology, 1988, 8:1247-1252). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of derivatives encompassed in the scope of the claims one skilled in the art would be forced into undue experimentation in order to practice broadly the claimed invention.

It is **not** routine in the art to screen for positions within the protein's sequence where amino acid modifications (i.e. additions, deletions, or modifications) can be made with a reasonable expectation of success in obtaining similar activity/utility are limited in any protein and the result of such modifications is unpredictable based on the instant disclosure (see Bowie et al, Science, Vol. 247, pp 1306-1310, especially p. 1306, column 2, paragraph 2 and Kumar et al, PNAS 87: 1337-1341 February 1991. One skilled in the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g. multiple deletions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acids modification in such proteins. The specification does not support the broad scope of the claims, which encompass a multitude of polypeptides because the specification does **not** disclose the following:

- the general tolerance to modification and extent of such tolerance;
- specific positions, which can be predictably modified;
  -which regions are protective; and
- essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have **not** provided sufficient guidance to enable one skilled in the art to make and use the claimed polypeptides in manner reasonably correlated with the scope of the claims broadly including any number of deletions, additions, substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986).

The specification does not support the broad scope of the claims which encompasses all variants of the polypeptide and the possibility of changing one or more amino acids to any one of 23 different amino acids because the specification does not disclose the following: the general tolerance to modification (substitution, insertion, deletion) and extent of such tolerance; specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical; what variants/analogs, if any, can be made which retain the biological activity, claimed vaccine protection of the polypeptide; and the specification provide essentially no guidance as to which of the essentially infinite possible choices is likely to be successful. Further, Houghten et al (Vaccine 86, 1986, pp. 21-25)

teach that changes/modifications (addition, substitution, deletion or inversion) of one or more amino acids in a polypeptide will alter antigenic determinants and therefore effect antibody production (p. 21) as well as antibody binding. Houghten et al also teach that "... combined effects of multiple changes in an antigenic determinant could result in a loss of [immunological] protection." and "A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies..." (p. 24). Houghten et al teach that point mutations at one key antigen residue could eliminate the ability of an antibody to recognize this altered antigen (p. 24). It is not always possible to make the variants/analogs or derivatives that retain immunodominant regions and immunological activity if the regions have been altered. It is known in the art that amino acid changes/variations of a peptide will affect its properties; "... alterations in the chemical nature of an amino acid within a site (e.g., reversal, removal or creation of a charge, elimination of a hydrogen bond, etc.) brought about by chemical modifications or evolutionary replacement in a homologous protein of a different species would reduce or abolish the reactivity of the site." (Bixler et al, Synthetic Vaccines, Volume 1, 1987, pp. 39-71, p. 56, para. 1). The determination of substitutions, deletions, and other undescribed and/or undefined "modifications" that result in analogs or derivatives which retain the immunological activity of the polypeptide would require undue experimentation for a person of ordinary skill in the art. See M.P.E.P. §§ 706.03(n) and 706.03(z).

The amount of direction or guidance presented in the specification and the absence of working examples, of the claimed polypeptides of the vaccine, is a hindrance to practicing the claimed invention. Applicants have not provided guidance in the specification toward the broad scope of the variants of the claimed polypeptide as well as the broad scope of protection against any and all pneumococcal infections. One skilled in the art would not accept on its face in view of the lack of examples given in the specification as being representative of the success in making and using the claimed invention in view of the lack of guidance in the specification and the known unpredictability associated with the ability to predict the biological effects exerted by the variants of the polypeptides as well as protection against all pneumococcal infections. The quantity of experimentation required to practice the invention as claimed would require the de novo determination of accessible target sites, modes of delivery and formulations of the claimed vaccine. Since the specification fails to provide particular guidance

for the making and use of the vaccine and the art teaches that this is not yet possible (i.e. highly unpredictable), it would require undue experimentation to practice the invention as presently claimed.

Further, the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art and the level of skill in the art. The state of the art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. The specification must be enabling as of the filing date, not evidence provided several years after the date of filing. The state of the art for a given technology is not static in time. It is entirely possible that a disclosure filed on January 2, 1990, would not have been enabled. However, if the same disclosure had been filed on January 2, 1996, it might have enabled the claims. Therefore, the state of the prior art must be evaluated for each application based on its filing date. (see MPEP 2164.05(a))

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims is quite broad in view of the scope of the possible polypeptides as well as the scope of pneumococcal infections. The nature of the invention and the state of the art has been described above. The level of one of ordinary skill is high (PhD level). The art is unpredictable as previously indicated. With regard to factors 6 and 7, the specification does not provide sufficient direction and the working examples do not enable the broad scope of the claimed invention; which in turn would require undue experimentation to practice the claimed invention. A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). In

view of all of the above, the pending specification does not enable the claimed invention and therefore the pending claims are not enabled.

The rejection is maintained for the reasons of record. Applicant's arguments filed October 12, 2007 have been fully considered but they are not persuasive.

Applicants have asserted that claim 15 has been amended to recite that the vaccine protects against the R6x pneumococci and type 4 pneumococci, that the specification teaches that polypeptides from the type 4 pneumococci serotype provide a cross-protective effect against the R6x strain and therefore the instant claims are enabled under 35 U.S.C. § 112, first paragraph, and the rejection of the claims should be withdrawn. Applicants have also argued that a structural/functional analysis of SEQ ID NO: 4 and SEQ ID NO: 3 allows one of skill in the art to conclude that it is Domain A in SEQ ID NO: 3 (which shares 96% similarity to SEQ ID NO: 4) that is conferring the cross-protective effect to serotype R6x. Applicants have asserted that SEQ ID NO: 3 has three regions (an N-terminal region, Domain A and Domain B) and that SEQ ID NO: 4 comprises Domain C. Applicants have asserted that Domain C shares 96% similarity to Domain A. Further, Applicants have SEQ ID NO: 3 was shown to provide a protective effect against serotype R6x, such an effect would occur via conserved epitopes shared between the CbpA proteins from both serotypes. Applicants have asserted that in view of the structural and functional studies performed, one of skill in the would accept that SEQ ID NO: 4 would provide a protective effect against both the R6x serotype and the Type 4 serotype.

However, it is noted that SEQ ID NO: 4 (106 amino acids) is less that half the size of SEQ ID NO: 3 (284 amino acids), is there evidence that indicates that the portion of SEQ ID NO: 3 that is similar to SEQ ID NO: 4 is the portion of the polypeptide that contains the epitopes and/or confers protection against pneumococcal infection. It is not clear from Applicants' arguments that SEQ ID NO: 4 would be protective against either R6x serotype or the Type 4 serotype of *Streptococcus pneumoniae*. Applicants have not shown that the other 284 amino acids of SEQ ID NO: 3 did not provide the protective effect taught in the specification. Applicants have not shown that the portions of SEQ ID NO: 3 and SEQ ID NO: 4 that are the same actually contain the epitope or portion of the protein that is protective.

The specification does not support the broad scope of the claims which encompasses all variants of the polypeptide and the possibility of changing one or more amino acids to any one of 23 different amino acids because the specification does not disclose the following: the general tolerance to modification (substitution, insertion, deletion) and extent of such tolerance; specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical; what variants/analogs, if any, can be made which retain the biological activity, claimed vaccine protection of the polypeptide; and the specification provide essentially no guidance as to which of the essentially infinite possible choices is likely to be successful. Further, Houghten et al (Vaccine 86, 1986, pp. 21-25) teach that changes/modifications (addition, substitution, deletion or inversion) of one or more amino acids in a polypeptide will alter antigenic determinants and therefore effect antibody production (p. 21) as well as antibody binding. Houghten et al also teach that "... combined effects of multiple changes in an

antigenic determinant could result in a loss of [immunological] protection." and "A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies..." (p. 24). Houghten et al teach that point mutations at one key antigen residue could eliminate the ability of an antibody to recognize this altered antigen (p. 24). It is not always possible to make the variants/analogs or derivatives that retain immunodominant regions and immunological activity if the regions have been altered. It is known in the art that amino acid changes/variations of a peptide will affect its properties; "... alterations in the chemical nature of an amino acid within a site (e.g., reversal, removal or creation of a charge, elimination of a hydrogen bond, etc.) brought about by chemical modifications or evolutionary replacement in a homologous protein of a different species would reduce or abolish the reactivity of the site." (Bixler et al, Synthetic Vaccines, Volume 1, 1987, pp. 39-71, p. 56, para. 1). The determination of substitutions, deletions, and other undescribed and/or undefined "modifications" that result in analogs or derivatives which retain the immunological activity of the polypeptide would require undue experimentation for a person of ordinary skill in the art. See M.P.E.P. §§ 706.03(n) and 706.03(z).

The Wands factors include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims is quite broad in view of the scope of the possible polypeptides as well as the scope of pneumococcal infections. The nature of the invention and the state of the art has been described above. The level of one of ordinary skill is high (PhD level). The art is unpredictable as previously indicated. With regard to factors 6 and 7, the specification does not provide sufficient direction and the working examples do not enable the broad scope of the claimed invention; which in turn would require undue experimentation to practice the claimed invention. A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). In view of all of the above, the pending specification does not enable the claimed invention and therefore the pending claims are not enabled.

5. No claims are allowed.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will

be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-8975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

N. M. Minnifield
Primary Examiner
Art Unit 1645

NMM
January 22, 2008